

Poster Session I

Campath-1H (alemtuzumab) is used during conditioning to prevent graft-versus-host disease and improve engraftment. Pharmacokinetic data have shown that a commonly employed dose of alemtuzumab (20 mg/day x 5, total dose 100 mg) results in potentially lympholytic alemtuzumab levels for >50 days post-transplant. Delayed alemtuzumab clearance might contribute to increased incidence of viral infections. We therefore studied the effect of a reduced dose of alemtuzumab (20 mg/day x 2, total dose 40 mg) on CMV reactivation. Nine patients (6 male, 3 female; median age 41 yrs, range 22-55 yrs) underwent allogeneic stem cell transplantation (7 MUD, 2 MRD) for a variety of hematologic malignancies after conditioning with thiotepe/TBI/alemtuzumab (7 patients) or fludarabine/melphalan/alemtuzumab (2 patients). Five patients were at risk for CMV reactivation (patient or donor CMV seropositive). Alemtuzumab was administered IV on day -5 and -1 prior to stem cell infusion. CMV reactivation was checked weekly by CMV pp65 antigenemia testing in at-risk patients. All patients received leukocyte depleted blood products (third generation filter). All patients engrafted. Four out of five patients at-risk (80%) developed CMV reactivation at a median of 28 (range 17-32) days post-transplant. No CMV infection occurred in low-risk patients (patient and donor both CMV seronegative). CMV reactivation was treated with IV ganciclovir induction for a minimum of two weeks, followed by IV or PO (val)ganciclovir maintenance. Two patients had a febrile illness at the time of CMV reactivation, however no evidence of CMV disease was found on imaging studies and/or biopsies. Repeated reactivation occurred in two patients, and was responsive to retreatment with ganciclovir or foscarnet with the addition of IVIG. No patient died from CMV related complications. We conclude that early CMV reactivation remains a frequently encountered problem after conditioning regimens containing reduced dose alemtuzumab. CMV prophylaxis should be considered in at-risk patients.

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SEX STEROID ABLATION THERAPY RESTORES THYMIC FUNCTION AND ENHANCES HEMOPOIESIS AND LYMPHOPOIESIS FOLLOWING ALLOGENEIC AND AUTOLOGOUS STEM CELL TRANSPLANTATION

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Opportunistic infection, morbidity and mortality are common following HSC transplantation because of the failure to regenerate an adequate immune system. This is due to the severe sex steroid induced thymic atrophy that occurs with age. Using surgical or temporary chemical (LHRH/GnRH) castration we have shown that blocking sex steroids profoundly enhances thymus function and immune capacity in adult and aged mice. This involved triggering proliferation of the early thymocyte precursors, reduction of apoptotic cells and restored thymic architecture. In addition, in mouse BMT models there was a significant enhancement of BM function and levels therein of HSC in castrated mice. The HSC were readily incorporated into the marked regeneration of the thymus. Thus, sex steroid ablation enhances immune regeneration both at the HSC (BM) and intrathymic levels. We then examined prostate cancer patients undergoing routine sex steroid ablation therapy. They had a significant increase in blood T lymphocytes (importantly CD4+ naive TREC+) and NK cells, by 4-months post-treatment. This lead to clinical trials using an LHRH agonist to ablate sex steroids in patients receiving allogeneic or autologous peripheral blood HSC transplantation (PBST). Compared to control patients (no LHRH-A treatment), there was firstly a significantly decreased time to engraftment with both autologous and allogeneic PBST LHRH-A recipients showing significant increases in neutrophil counts, total WBC and lymphocyte

counts within the first month post-transplant compared to controls. In addition there was a significant increase in CD34+ stem cell numbers and NK cells in the autologous transplant recipients who had received the LHRH-A. Importantly the allogeneic recipients in particular showed an increase in total and naive (CD45RA+CD62L+CD45RO-; TREC+)T cell numbers in the blood at all time-points post-transplant compared to controls. Patients receiving the LHRH-A treatment also demonstrated a significantly increased in vitro proliferative responsiveness to TCR stimulation and Tetanus Toxin. These studies set a fundamentally new approach for the treatment of many clinically based T-cell disorders.

LEUKEMIA

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BONE MARROW ANGIOGENESIS DECREASES AFTER STEM CELL TRANSPLANTATION FOR TREATMENT OF LEUKEMIA

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Background: Bone marrow transplantation is an important mode of therapy in adult leukemia patients. Increased bone marrow angiogenesis is shown to participate in the progression of leukemia by direct stimulatory effect of the cytokine secreted by endothelial cells on the proliferation of leukemia cells, thus the bone marrow angiogenesis might be a contributory factor in relapse and also response to therapy. Previous studies have shown that bone marrow angiogenesis might decrease after stem cell transplantation in multiple myeloma patients. **Aims:** To study whether bone marrow transplantation for the treatment of leukemia affects the bone marrow vascular density and to clarify its clinical significance. **Materials and methods:** Pre- and post-transplant (30 days after transplantation) bone marrow biopsy samples of 13 patients (3 autologous, 10 allogeneic) including 9 AML and 4 ALL patients were evaluated using immunohistochemical staining for vWF. All the vessels in the bone marrow biopsy core were counted and results were corrected for the bone marrow biopsy length. The correlation between the degree of decrease in angiogenesis and relapse and Graft-Versus-Host-Disease was also studied. **Results:** The bone marrow angiogenesis was significantly decreased after one month of chemotherapy (Mean pre-transplant vascular number = 5.6/mm +/- 0.9 SEM, Mean post-transplant vascular number = 1.6/mm, +/- 0.26 SEM, P < 0.001). There was no correlation between the degree of angiogenesis and bone marrow cellularity (which returned to near-normal levels at the time of post-transplant biopsy). The changes in bone marrow vascular density also did not correlate with the type of transplant, relapse or the occurrence of Graft-Versus-Host-Disease. **Discussion:** A significant and robust decrease in the bone marrow angiogenesis after stem cell transplantation for leukemia was shown. This might be a contributing factor in excellent results of bone marrow transplantation for leukemia by decreasing proliferation stimulatory cytokines from the endothelial cells. The lack of correlation between relapse and decrease in bone marrow density might be attributable to the multifactorial nature of relapse in leukemia.

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AML TRANSPLANTATION: AUTOLOGOUS VS ALLOGENEIC

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